REMARKS

The final Office Action mailed on March 07, 2007 has been received and its contents carefully considered.

In this Amendment, paragraphs [0039] and [0043] have amended for improved clarity. Support is discussed in the following. Claim 1, 12, 15, 18, 19, 21, 30, 33, 36 and 37 have been amended, and new dependent claims 39-44 have been added to further protect the invention. Support is discussed in the following. To the best of the undersigned attorney's information and belief, these changes do not introduce any new matter into the Application.

The section deleted from paragraph [0043] has been inserted into paragraph [0039] with certain changes. Support for the amendment of paragraph [0039], and for the amendment of claims 1 and 21 to recite, "a molar ratio of the first phospholipid to the second phospholipid is ~~larger~~ no less than ~~1/20~~ 3/16" is found in paragraphs [0037] to [0039], and Tables 3 and 4.

Claims 1-44 are pending in the Application. Claims 1 and 21 are written in independent form. For at least the following reasons, it is submitted that this Application is in condition for allowance.

I. The Examiner has objected to the Amendment filed December 4, 2006 under 35 U.S.C. §132(a). In response thereto, the disclosure has been amended to correct the informalities specifically noted by the Examiner. In view of these amendments, Applicants request that this objection be withdrawn.

II. The Examiner has rejected claims 12-19 and 30-37 under U.S.C. §112, second paragraph , as being indefinite for failing to point out and distinctly claim the subject matter. This rejection is submitted to be moot in view of the amendments made herein to the claims. For example, claim 37 has been amended to use a close-ended expression, i.e., "selected from the group consisting of" to clearly define the scope of the cholesterol derivatives. Claims 12, 15, 18, 19, 30, 33 and 36 have also been amended in the same manner. Accordingly, the claimed derivatives of compounds no

longer may be said to lead to a plethora of compounds, so that the metes and bounds of the claims are submitted to be clear. It is therefore respectfully requested that this rejection be withdrawn.

III. The Examiner has rejected claims 12-18 and 30-36 under U.S.C. §112, first paragraph. Claims 12, 15, 18, 19, 30, 33, 36 and 37 have been amended to encompass a group of compounds using close-ended terminology and therefore have definite scopes. Moreover, the disclosure is submitted to support the claimed groups of compounds. Thus, Applicants submit that one of ordinary skill in the art would find sufficient guidance in the Application to practice the claimed invention without any undue experimentation. It is therefore respectfully requested that this rejection be withdrawn.

IV. The Examiner has rejected claims 8-12, 15, 18, 19, 26-30, 33, 36 and 37 under U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In response to the Examiner's position, these claims have been amended and are now submitted to find support in the Application as filed and to comply with the written description requirement. It is therefore respectfully requested that this rejection be withdrawn.

V. The Examiner has rejected claims 1-9, 18 and 19 under 35 U.S.C. §102(b) as being anticipated by Straubinger et al. (US 5,415,869).

VI. The Examiner has rejected claims 1-7, 19, 21-25 and 37 under 35 U.S.C. §102(b) as being anticipated by Scotto et al. (US 4,873,089).

VII. The Examiner has rejected claims 1-3, 5-9, 15, 16, 18 and 19 under 35 U.S.C. §102(b) as being anticipated by Castor et al. (US 5,776,486).

Claims 1, 12, 15, 18, 19, 21, 30, 33, 36 and 37 have been amended, and it is submitted that amended independent claims 1 and 21, as well as the claims 2-20 and

22-42 dependent there from, are patentably distinguishable over the cited references for at least the following reasons.

It is well settled that a reference may anticipate a claim within the purview of 35 U.S.C. § 102 only if all the features and all the relationships recited in the claim are taught by the reference either by clear disclosure or under the principle of inherency.

Amended independent claim 1 is directed to a formulated liposome for incorporating high content of hydrophobic substances comprising a first phospholipid, a second phospholipid, one or more hydrophobic substances and liposome-forming materials. The first phospholipid is selected from a hydrogenated naturally-occurring phospholipid or a saturated phospholipid with long carbon chains (-$(CH2)_n$-, the value of n is at least 14); and the second phospholipid is selected from an unsaturated phospholipid or a saturated phospholipid with short carbon chains (-$(CH2)_n$-, the value of n is at most 14). The first and the second phospholipids coexist in the liposome in two immiscible phases and create several discontinuous regions, and a molar ratio of the first phospholipid to the second phospholipid is no less than 3/16 (supported by paragraphs [0037] to [0039], and Tables 3 and 4). Also, a phase transition temperature T_{g1} of the first phospholipid is in the range between 40 and 74 °C, and a phase transition temperature T_{g2} of the second phospholipid is in the range between –30 and 10 °C while a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges subject to an order of $T_{g1} > T_1 > T_2 > T_{g2}$.

Amended independent claim 21 is directed to a liposome for incorporating high content of hydrophobic substances comprising a first phosphatidyl choline, a second phosphatidyl choline, one or more hydrophobic substances and liposome-forming materials. The first phosphatidyl choline is selected from a hydrogenated naturally-occurring phospholipid or a saturated phospholipid with long carbon chains (-$(CH2)_n$-, the value of n is at least 14); and the second phosphatidyl choline is selected from an unsaturated phospholipid or a saturated phospholipid with short carbon chains (-$(CH2)_n$-, the value of n is at most 14). The first and the second phosphatidyl cholines coexist in the liposome in two immiscible phases and create several discontinuous regions, and a molar ratio of the first phosphatidyl choline to the second phosphatidyl choline is no less than 3/16. Also, a phase transition temperature T_{g1} of the first phosphatidyl choline is in the range between 40 and 74℃, and a phase transition

temperature T_{g2} of the second phosphatidyl choline is in the range between –30 and 10 ℃, and a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges subject to an order of $T_{g1} > T_1 > T_2 > T_{g2}$.

Straubinger et al. disclose a pharmaceutical formulation comprising one or more negatively charged phospholipids and one or more zwitterions phospholipids. However, Straubinger et al. do not disclose (or otherwise suggest) that a molar ratio of the first to second phospholipids of the formulated liposome is no less than 3 to 16. Therefore, the liposomes of the present invention are able to incorporate very high contents of paclitaxel, such as **25 mole%** paclitaxel, and remain stable for at least 60 days (Table 3). On the contrary, Straubinger's formulated liposomes remain physically stable for 75 days if they contain no more than **2.1%** of taxol (see FIG. 5 and Example 2). Thus, Straubinger et al. fail to teach or suggest a liposome formulation in accordance with the claimed invention for incorporating a high content of hydrophobic substances. As such, it is submitted that Applicants' independent claim 1, and the claims dependent there from, claims 2-9, 18 and 19, are patentably distinguishable from, not anticipated by, and not obvious in view of Straubinger et al. so that the rejection under 35 U.S.C 102(b) should be withdrawn.

Scotto et al. disclose a process for the preparation of fusogenic proteolipsomes. However, Scotto et al. do not disclose (or otherwise suggest) that the formulation for lipsomes with a molar ratio of the first to second phospholipids of the formulated liposome as being no less than 3 to 16, for incorporating a large amount, such as (ex: 25 mole% paclitaxel) of hydrophobic substances. Besides, Scotto et al.'s formulation is used for incorporating proteins, and is not directly used for incorporating the hydrophobic substances. As such, it is submitted that Applicants' independent claims 1 and 21, and the claims dependent there from, claims 2-7, 19, 22-25 and 37, are patentably distinguishable from, not anticipated by, and not obvious in view of Scotto et al. so that the rejection under 35 U.S.C 102(b) should be withdrawn.

Castor et al. disclose phospholipid materials containing fresh chicken egg yolk and soy bean phosphatidylcholine, wherein chicken egg yolk consisted of 60% phosphatidyl choline (PC) and 16.5% phosphatidyl ethanolamine (PE) (col. 23, line 10-line 15). Egg yolk is an unpurified EPC, and both of PE and soy bean PC are unsaturated phospholipids. Castor et al. do not disclose (or otherwise suggest) that a

first and second phospholipids are required and restricted in the limitation of molar ratio of 3 to 16. As such, it is submitted that Applicants' independent claim 1, and the claims dependent there from, claims 2-3, 5-9, 15, 16, 18 and 19, are patentably distinguishable from, not anticipated by, and not obvious in view of Castor et al. so that the rejection under 35 U.S.C 102(b) should be withdrawn.

VIII. Moreover, the Examiner has rejected claims 20 and 38 under 35 U.S.C. §102(a) [sic 103] as being unpatentable over Scotto et al (US 4,873,089) in view of Crosasso et al.

IX. The Examiner has also rejected claims 1-19 and 21-37 under 35 U.S.C. §102(a) [sic 103] as being unpatentable over Scotto et al (US 4,873,089) in view of Unger et al (US 5,733,572) and Castor et al (US 5,776,486).

Independent claims 1 and 21 have been amended. It is submitted that these claims are *prima facie* patentably distinguishable over these references, taken alone or in combination, for at least the following reasons.

It is well-settled law that in order to properly support an obviousness rejection under 35 U.S.C. §103, there must have been some teaching in the prior art to suggest to one skilled in the art that the claimed invention would have been obvious. *W. L. Gore & Associates, Inc. v. Garlock Thomas, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983).

None of the cited references, including Scotto et al.,Crosasso et al., Unger et al, and Castor et al., are submitted to **teach or suggest** the lipsome formulations defined in the claimed invention, in particular the molar ratio of the first to second phospholipids of the formulated liposome as being no less than 3 to 16, for incorporating high contents of hydrophobic substances in the liposomes. Also, the storage stability of the liposome incorporating high contents of hydrophobic substances, as in the claimed invention, is greatly improved (see Table 3 of the claimed invention). Applicants submit that Applicants' liposome formulation is beyond the teachings of the cited references, and the advantages cannot be achieved by combining the disclosures in the cited references. Thus, it is submitted that it these combinations of references do not meet Applicants' claims so that no *prima facie* case of obviousness has been made out.

Further, the modifications needed to meet Applicants' claims would not be obvious to a person of ordinary skill in the art.

CONCLUSIONS

In view of the foregoing amendments and arguments, it is submitted that claims 1-44 and the Application are in condition for allowance. Such action and the passing of this case to issue are requested.

Should the Examiner consider that a conference would help to expedite the prosecution of this Application, the Examiner is hereby invited to contact the undersigned counsel to arrange for such an interview.

The amount of $1,090.00 is attached by way of credit card form PTO-2038, for payment of the RCE fee ($790.00) and additional claim fee ($300.00 to cover six (6) dependent claims in excess of the 38 total claims previously paid). Should the remittance be accidentally missing or insufficient, or should any additional fee be deemed due, the Commissioner is hereby authorized to charge such fee to our Deposit Account No. 18-0002 and is requested to advise us accordingly.

Respectfully submitted,

June 7, 2007

Date

Steven M. Rabin
Reg. No. 29,102

RABIN & BERDO, PC
Cust. No. 23995
Facsimile: 202-408-0924
Telephone: 202-371-8976

SMR/AJW:ac